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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/189,130	11/10/98	HOUCK J	47.653.1

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EXAMINER	
BORIN, M	
ART UNIT	**PAPER NUMBER**
1631	11

DATE MAILED: 01/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/189,130	Houck et al.
Examiner	**Group Art Unit**
M. Borin	1631

☒ Responsive to communication(s) filed on *Sep 3, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) *9-23* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status of Claims

1. Acknowledgment is made of the amendment filed 09/03/99 (paper # 9). Claim 2 is amended. Claims 1-23 are pending. Claims 1-8 are under consideration; claims 9-23 remain withdrawn from further consideration by the examiner. Cancellation of claims 9-23 as drawn to non-elected group is requested.

2. Applicants arguments with respect to rejection made under 35 U.S.C. 103 have been considered and are addressed in the following discussion of each rejection. In addition new grounds of rejection under 35 U.S.C. §112, first paragraph, are made herewith.

Claim Rejections - 35 U.S.C. § 103.

3. Claim 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode alone or in view of Gleisner

The instant claims are drawn to pharmaceutical composition comprising a formyl Met peptide having formula f-Met-Leu-X, wherein X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe, and Phe-Tyr. In particular, the formyl Met peptide analog is f-Met-Leu-Phe-Phe (claim 2) or f-Met-Leu-Tyr (claim 3).

It is well known in the art that biological mediators such as chemotactic factors stimulate the migration of neutrophils from circulation into sites of infection or tissue damage. These mediators are

also believed to increase cell adhesion to injured sites and to activate neutrophils to release toxic agents such as oxygen metabolites and proteases.

In particular, Kermode et al. teach that neutrophils play a major role in body's defense mechanism against infectious microorganisms and that biological responses of these cells can be triggered by chemotactic formyl Met peptides. The reference discloses that formyl Met peptides, such as f-Met-Leu-Phe, f-Met-Leu-Phe-Phe and f-Nle-Leu-Phe-Tyr, bind to specific receptors on neutrophil membranes and elicit neutrophil degranulation. In particular, f-Met-Leu-Phe-Phe (i.e., peptide of the instant claim 2) is one of the most potent formyl Met peptides analogs. Degranulation response is well correlated with the receptor binding. See p.276, first paragraph; Tables 1,2; Fig.2;p. 719. Kermode teaches that the rabbit peritoneal neutrophils used in the study are an adequate *in vitro* model as they have proved suitable for detailed biological characterization of the biological responses of neutrophils to chemotactic peptides. See p. 1991, left column, last paragraph.

Similarly to Kermode reference, Ferry et al. teaches that multiple effects of formyl Met peptides include adhesion, chemotaxis, superoxide production and lysosomal enzyme release in neutrophil leukocytes. See p. 61, first paragraph. In particular, the reference teaches formyl Met peptide, f-Met-Leu-Tyr (i.e., peptide of the instant claim 3).

The above references differ from the presently claimed invention by failing to explicitly disclose the use of formyl-Met peptides as pharmaceuticals.

It would have been *prima facie* obvious to one of ordinary skill in art at the time the invention was made to be motivated to make and use pharmaceutical composition comprising formyl-Met

peptides, in particular f-Met-Leu-Phe-Phe and f-Met-Leu-Tyr taught by Kermode, because the reference both references teach that formyl-Met peptides possess useful biological properties as they stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms. One would expect that *in vitro* observations of the effect of formyl-Met peptides on neutrophils will be translated into similar *in vivo* effect, because Kermode teaches that the rabbit peritoneal neutrophils is an adequate *in vitro* model as they have proved suitable for detailed biological characterization of the biological responses of neutrophils to chemotactic peptides.

Further, it is well known that pharmaceuticals are usually dispensed in either liquid or solid carriers. One of primary skills in the art would have known that compound "X" would have had to be formulated in some manner so as to make it useful pharmaceutically.

Response to arguments

Applicants argue that neither Kermode nor Ferry suggest to use formyl peptides as pharmaceuticals. However, the knowledge that formyl peptides stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms would be a sufficient motivation to an artisan to apply such agent as a pharmaceutical under conditions when therapeutic stimulation of such defense reaction to infectious microorganisms is required. The rationale to support a rejection under 35 U.S.C. 103 may rely on logic and sound scientific principle. "In considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to

draw therefrom." In re Preda , 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). An artisan will be fully aware that agents that stimulate neutrophil functions can be either useful in appropriate controlled conditions, or harmful when they are being used or exogenously released in such amounts or under such conditions that they cause an undesirable inflammatory reaction. An illustration of the latter is the observation of Ferry et al (which is used by the applicant as a showing of undesirable inflammatory effect of f-met peptides) that infusion of f-met peptides causes disorders such as colitis. Note, however, that the reference specifies that in such experiments the dosage of f-met peptides was in a very high millimolar range, i.e. at least three orders of magnitude higher than physiological (see p. 64, Discussion section, end of second paragraph).

An example of an agent which, similarly to f-met peptides, can be either harmful or useful is colony-stimulating factor (CSF). Effects of CSF are similar to those of formyl peptides. See, e.g., Beaulieu et al., Wright et al.. CSF is one of the leading mediators of inflammation. See, e.g., al-Janadi et al. At the same time CSF is being used to treat inflammation. See, e.g., Burak et al.

4. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode and Ferry, supra in view of Anderson. Two peptides encompassed by the instant claim, which have not been considered in the preceding rejection and which are not explicitly taught in the primary references, are f-Met-Leu-Phe-Tyr and f-Met-Leu-Tyr-Phe.

Anderson teaches that the requirements for the core structure of biologically active formyl Met peptide analogs are the following: N-acyl formyl group, a Met or Nle residue in position 1, Leu,

Val or Ile residue in position 2, and an aromatic amino acid in position 3; a formyl Met peptide analog can be either a tripeptide or a tetrapeptide. See p. 253, Discussion section, first paragraph. As an example, Anderson teaches such formyl Met peptides as f-Met-Leu-Phe, f-Met-Leu-Tyr. See Table 2.

In regard to the instantly claimed peptide f-Met-Leu-Phe-Tyr, it would have been *prima facie* obvious to one of ordinary skills in art at the time the invention was made to be motivated to substitute Nle for Met residue in position 1 of the peptide f-Nle-Leu-Phe-Tyr reported by Kermode, because Anderson teaches that biological activity of the peptides is retained when the residue in position 1 is either Nle or Met. One would expect that formyl Met peptide analog obtained by such substitution would have the same biological properties, i.e., activate functions of neutrophils.

In regard to the instantly claimed peptide f-Met-Leu-Tyr-Phe, it would have been *prima facie* obvious to one of ordinary skills in art at the time the invention was made to be motivated to substitute Phe for Tyr residue in position 3 of the peptide f-Nle-Leu-Phe-Phe reported by Kermode, because Anderson teaches that the residue in position 3 can be an aromatic amino acid, such as Phe or Tyr (see examples in Anderson, Table 2, lines 1, 2). One would expect that formyl Met peptide analog obtained by such substitution would have the same biological properties, i.e., activate functions of neutrophils.

Response to arguments

Applicants have traversed the secondary references pointing to the differences between the claims and the disclosure in the reference. Applicant is respectfully reminded that the rejection is

under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. It has been well established that the test for combining references is not what individual references themselves suggest but what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. Anderson was cited to demonstrate teaching of representatives of family of f-met peptides, described in general, e.g., in Freer reference (cited as prior art of record in the previous Office action).

5. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gleisner in view of Kermode, Ferry, and Anderson. The above rejections over Kermode, Ferry, and Anderson emphasized that it would be obvious to use chemotactic formyl Met peptides as pharmaceuticals to trigger body's defense mechanisms because they stimulate neutrophil degranulation and other responses. Gleisner, on the other hand, teaches that formyl Met peptides can be also useful to counter an existing inflammation because, in the presence of other inflammatory agents which themselves cause neutrophil granule release, the formyl Met peptides inhibit neutrophil granule release and histamine release caused by other "degranulators". Accordingly, the Gleisner reference provides motivation to one of ordinary skills in the art to formulate pharmaceutical compositions of formyl Met peptides to prevent degranulation of mast cells in the course of inflammatory disorders and thus to inhibit cytokine/histamine release which is a desirable pharmacological effect. Kermode, Ferry and Anderson teach various representatives of f-met peptides as discussed above.

Response to arguments

Applicants argue that it is not obvious that structurally similar compounds will have the same effect or potency. No factual evidence has been presented showing that other representatives of the known family of structurally similar f-met peptides will differ in their activity to the extent that they will be expected not to have the same type of activity. While it may not be absolutely certain that different representatives of the family of f-met peptides will be as effective in the prevention of mast cell degranulation as f-Met-Leu-Phe described in Gleisner, a *prima facie* case of obviousness does not require absolute predictability of success. See In re O'Farell, 7 USPQ2d 1673 (CAFC 1988). Applying structural and functional analogs of the peptide used in Gleisner would not have been expected to lower the probability of successful treatment of mast cell degranulation.

6. Claims 1, 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode, Ferry, Anderson , and Gleisner as applied to claims 1-3 in the rejections above, and further in view of Goodman and Gilman.

Claims 4-8 are drawn to routes of administration (oral, inhalation, aerosol, topical, or tablet). Selection of a route of administration and appropriate carriers is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. See, e.g., Goodman and Gilman, p. 4-9.

Claim Rejections - 35 U.S.C. § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions having pharmaceutical effect to inhibit mast cell degranulation caused by other inducers of the degranulation, does not reasonably provide enablement for pharmaceutical use of f-met peptides in general.

The invention is drawn to pharmaceutical compositions comprising a formyl Met peptide ; the scope of the invention encompasses any dosage of f-met peptides in such composition. It is well known in the prior art that f-met peptides are predominantly known for their inflammatory effect. See the applicants arguments presented in paper 39, which clearly present this point. Further, Ferry et al, as described in the art rejection above, teaches that the use of f-met peptides in high dosage results in an induced disorder (colitis). Thus, the prior art teaches that the effect of such agents can be the opposite to the pharmaceutical. The prior art is not predictable in regard to dosage range and conditions under which the f-met peptides would have pharmaceutical effect. The instant specification does not provide guidance for the selection of the range of pharmaceutical effect. The range 0.1 to 100,000 μg/kg a day, indicated on p. 11, encompasses 6 orders magnitude in the dosage which will most likely encompass both the ranges of inoperative and harmful effects. Further, the experimental data presented in the examples (see figures 2,3 are presented in different concentration

units (nMoles) and are not comparable with the above general dosage range. The working examples are limited to the demonstration of inhibition of induced mast cell degranulation caused by other inducers of degranulation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Conclusion.

8. No claims are allowed

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward can be reached on (703) 308-0254. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10. The Art Unit location of your application in the PTO has changed. To aid any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1631.

January 10, 2000

mlb

MICHAEL BORIN, PH.D
PATENT EXAMINER